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Review

Cardiotoxicity, strain: evidence to date

Cardiotoxicidad, strain: evidencia actual

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ABSTRACT. In the last decade there have been notable advances in the treatment of cancer. The introduction of targeted therapies has increased the rates of cure and remission in some of them. The net result is the emergence of a cohort of patients whose survival will be sufficient to cause cardiac side effects of the therapies used. In this review we will deal with the current knowledge about the mechanisms of cardiotoxicity, the traditional methods for its evaluation and the new strategies for its early detection.
Keywords: Cardiotoxicity, strain rate, echocardiography, oncology.

RESUMEN. *En la última década ha habido avances notables en el tratamiento del cáncer. La introducción de terapias dirigidas ha aumentado las tasas de cura y remisión en algunas de ellas. El resultado neto es la aparición de una cohorte de pacientes cuya supervivencia será suficiente para causar efectos secundarios cardiacos de las terapias utilizadas. En esta revisión trataremos el conocimiento actual sobre los mecanismos de cardiotoxicidad, los métodos tradicionales para su evaluación y las nuevas estrategias para su detección temprana.*
Palabras clave: *Cardiotoxicidad, strain rate, ecocardiografía, oncología.*

INTRODUCTION

Breast cancer in Mexico is the leading cause of death in women due to malignant neoplasms since 2,006; in Mexican women it represents 14% of deaths related to cancer.[1] According to estimates for 2030 of GLOBOCAN in Mexico, 24,386 women will have been diagnosed and 9,778 will die from breast cancer. Survival at 5 years in patients with breast cancer and access to oncological treatment in the public sector has been reported as 82% (95% CI, 81-84%), next few years a high number of women survivors of cancer with significant cardiovascular risk basal and/or secondary to multimodal oncological treatment (chemotherapy, white therapy and/or radiotherapy) received with curative oncological intent. The economic pressure for the Mexican public health system and the urgent need for care for cancer survivors in Mexico is a reality.[2-4] Estimates of disability-adjusted life years or DALYs (Disability Adjusted Life Years) from 2,006 to 2,016 have been reported in breast cancer; for women, breast cancer is the cancer with the highest incidence, mortality and DALYs (1.7 million incidents, 535,000 deaths and 14.9 million DALYs). A complex and costly picture of attention is expected in Latin American countries with limited resources.

It has been reported that breast cancer survivors have a 3-fold increased risk of developing heart failure within the first 5 years after cancer diagnosis compared to the general population.[5-7]

The term 'cardiotoxicity' is used to refer to LV dysfunction. The two main anticancer agents responsible for LV dysfunction are

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anthracyclines and targeted therapies (tyrosine kinase inhibitor, anti-human epidermal growth factor receptor 2, anti-vascular endothelial growth factor, proteasome inhibitors).[8-10] Recently, immune fulminant myocarditis was reported with the use of checkpoint immune inhibitors (anti-programmed cell death protein 1, anti-programmed cell death ligand 1, anti-cytotoxic T lymphocyte-associated protein 4), suggesting new cardiotoxicity pathways. LV dysfunction remains asymptomatic for a long time, but once symptomatic, the prognosis is one of the poorest in the heart failure population.[11-14]

CARDIOTOXICITY

The concept of left ventricular dysfunction induced by cardiotoxic chemotherapies is defined by a decrease in left ventricular ejection fraction (LVEF) of >10 percentage points to a value 15% of the global longitudinal strain are useful tools. According to the European Society of Cardiology, LVEF assessment can be performed by echocardiography (attempting to favour 3D LVEF), cardiac nuclear imaging and cardiac MRI.

Types of left ventricular dysfunction (LVD)

- **Type I:** due to cell death, whereby ventricular dysfunction and heart failure can occur years after antineoplastic treatment is concluded, it is dose dependent and implies worse prognosis (eg, anthracyclines);
- **Type II:** there is a compromise of myocyte function, without loss of these, for which ventricular dysfunction and heart failure are reversible, without leaving long-term sequelae (ex: trastuzumab).[15,16]

Initial cardiac evaluation prior to treatment and stratification of cardiotoxicity risk

To avoid the cardiotoxic effects to all patients who are going to undergo oncological treatment by radio or chemotherapy, a stratification of risk prior to treatment is performed, then follow-up is scheduled during the same and according to the results arise the measures to be taken through multidisciplinary assessment.

The initial assessment should consist of a history and physical examination aimed at assessing the presence of heart disease, ECG to detect arrhythmias or alterations in the QTc interval, echocardiogram and biomarkers for functional and structural assessment. Recommend healthy lifestyles, identify and establish a correct treatment for CVRF. Patients with CVRF present a higher risk of developing cardiotoxicity. CV risk factors are considered: unfavorable lifestyle (smoking, overweight and reduced physical activity) pre-existing diseases such as dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke or thromboembolic events. Patients with arrhythmias and ventricular dysfunction with EF lower than 50-55% are considered high risk group to develop cardiotoxicity with oncological treatment.

The guide of the American Society of Clinical Oncology (ASCO) in 2,016 developed guidelines for the prevention and monitoring of cardiac dysfunction in cancer survivors. This guide recommends that patients receiving the following treatment should be considered at high risk to develop cardiac dysfunction.[16,17]

Risk factors for cardiotoxicity

1. High doses of anthracyclines (eg: cumulative dose of doxorubicin greater than or equal to 250 mg/m^2, cumulative dose of epirubicin greater than or equal to 600 mg/m^2.
   - High doses of radiotherapy (greater or equal 30 Gy) with the heart within the treatment field.
   - Low doses of anthracyclines in combination with low doses of radiation with the heart in the irradiated area.
2. Treatment with low doses of anthracyclines or trastuzumab alone and the presence of one of the following CVRF:
   - Multiple FCRCV (greater or equal 2): smoking, obesity, HTA, DBT, DSLP during or after treatment.
   - Age greater than or equal to 60 years at the time of cancer treatment.
   - Commitment of cardiac function (LVEF 50-55%, antecedent of AMI, valvular disease of moderate degree) at any time before or after treatment.

3. Treatment with low doses of anthracyclines (<250 mg/m^2 ASC), followed by treatment with trastuzumab.[17]

Cardiovascular monitoring during treatment

Left ventricular ejection fraction (LVEF)

For years, LVEF was the only parameter monitoring method that detected cardiotoxicity, and multigated acquisition was the most common method used by oncologists. In the past 10 years, 2D and 3D echocardiography has become the standard for myocardial function assessment. 3D LVEF was shown to have the lowest temporal variability. A recent study of breast cancer patients has suggested that nadir LVEF values were identified by 3D echocardiography earlier than 2D echocardiography, suggesting that 3D measured LVEF might be a useful method to identify early cardiac injury. 3D LVEF and myocardial strain were associated with concurrent and subsequent changes in 2D LVEF, and concurrent change in diastolic function (E/e'). When adjusted for the respective 2D parameters, post-anthracycline 3D LVEF and global circumferential strain predicted subsequent 2D LVEF.[18-20]

Cardiac magnetic resonance (CMR) is particularly interesting in the cancer population, because of its spatial and temporal resolution, its reproducibility and accuracy for LVEF assessment. Recent evidence suggests that LV global circumferential strain and GLS measured with feature-tracking CMR may also identify early LV dysfunction. CMR also helps explain the decrease in LVEF and strain in cancer patients LV end diastolic volume due to decrease in preload (vomiting, diarrhea, sepsis leading to dehydration); therefore, LV end diastolic volume and LV end systolic volume should always be taken into account. CMR may facilitate our understanding for cardiotoxicity pathogenesis. Myocardial tissue changes, such as intracellular and interstitial edema, and fibrosis, may precede the alterations in LV volumes, reduction in LVEF, or changes in myocardial strain and may represent early markers of myocardial injury. Also, there is accumulating evidence of the presence of diffuse interstitial fibrosis (assessed by increased T1 mapping and extracellular volume fraction in anthracycline-induced cardiomyopathy), independent of cardiovascular comorbidities and associated with impaired diastolic function. There are also many etiologies of myocellular dysfunction that lead to LV dysfunction in patients receiving cardiotoxic chemotherapies that CMR can diagnose: myocarditis, stress-induced cardiomyopathy, myocellular injury and interstitial fibrosis.[21-23]

Deformation imaging by 2D echocardiography

Global longitudinal strain (GLS) is a strong predictor of cardiovascular morbidity and mortality in several cardiac diseases, and seems to be a consistent marker of cardiotoxicity. The expert consensus of the American Society of Echocardiography and the European Association of Cardiovascular Imaging considered a 15% reduction of GLS as a significant change to detect cardiotoxicity. In a small study of 44 patients treated with anthracycline and trastuzumab, Sawaya et al. showed that a 10% decrease of GLS combined with an increase of TnI from baseline to 3 months had an 83% positive predictive value and an 89% negative predictive value to detect cardiotoxicity (as defined as a symptomatic decrease >5% of LVEF with LVEF <55% or an asymptomatic decrease >10% with LVEF <55%).[24,25] Although the early detection of myocardial changes seems to be conceptually important, the real value of these changes lies in their capacity as prognostic markers of outcomes such as the same reduction in LVEF or the development of heart failure. The prognostic value has been evaluated in 8 studies involving about 452 patients (47 to 51 years old), most of them women with breast cancer, all of them received anthracyclines and most of them trastuzumab, the duration of follow-up was 12 to 15 months on average. A fall in the GLS of 10 and 15% predicted cardiotoxicity (including asymptomatic and symptomatic dysfunction).[26,27] The 95% confidence interval for the optimal cut-off value of the strain was 8.3 to 14.6%. On the contrary, the radial and circumferential deformation were not statistically significant

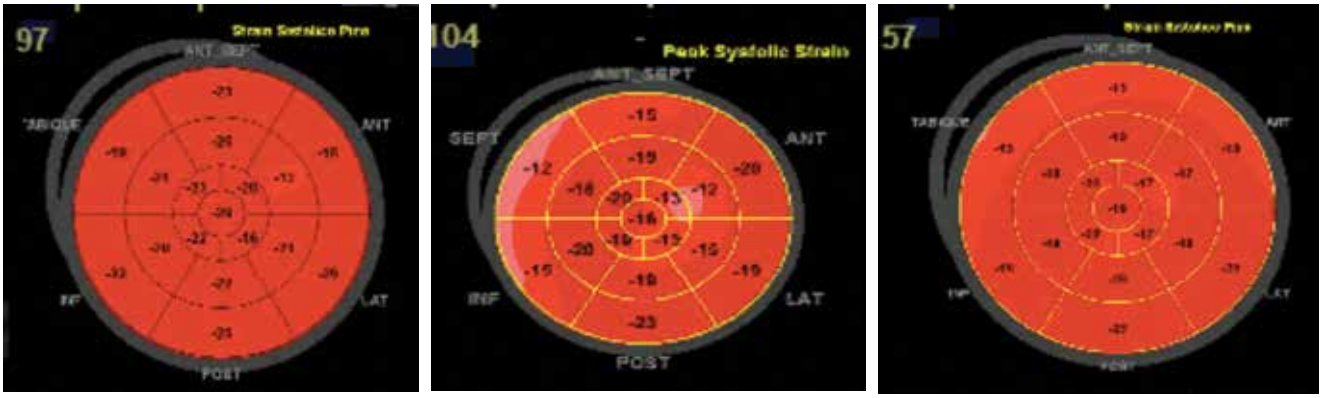
to predict cardiotoxicity. An interesting finding is that there is a combined parameter: DLG and LV torsion, which was the best prognostic marker of cardiotoxicity; this parameter provides information on subendocardic (DLG) and subepicardial (torsion) function, therefore this most sensitive measure of early myocardial changes should be evaluated in the future. Integrated biomarkers and cardiac imaging appears as a promising approach to precisely detect and predict cardiotoxicity. After chemotherapy regimens are completed, there are limited recommendations on appropriate follow-up in these patients. However, we must make several considerations, the first one that specifically the cardiotoxicity by anthracyclines can be detected several years after having concluded the therapy. There are 9 published studies of cases and controls that evaluated subclinical myocardial damage, approximately 436 patients, but none provided results with sufficient statistical significance, however in survivors treated with anthracyclines, a reduction in strain of 6.6 to 26% was demonstrated.[28]

Biomarkers

Cardinale and Sandri in 2003 evaluated a cohort of patients treated with high-dose chemotherapy, measuring cardiac troponin I (TropIc) before tx (basal) and at 0, 12, 24, 36 and 72 hours after the end of it. Those patients who had elevation of Troponin I (TropIc +) had a 12-month LVEF decrease of 18%, compared to the group that never had elevation of this marker (142 patients) where an average decrease of 2.5% was presented with a statistically significant difference between both. It is important to note that ventricular function gradually decreased over the 12 months that the study lasted, and that 20 of 57 patients who presented TropIc + did not show a decrease in LVEF, raising the question of whether the toxicity assessment cardiac echocardiography is a sufficiently sensitive method to distinguish those who will have a higher degree of cardiotoxicity. Early elevation (<72 h) of troponin I (TnI) (>0.08 ng/dL) has been demonstrated in up to one third of patients treated with anthracyclines.[29] The persistent elevation of the TnI during cancer treatment identifies patients with worse cardiovascular prognosis, who could benefit from ACEI treatment to reduce the risk of CVD without the need to suspend or modify the antitumor treatment. The current consensus of Dr. Plana recommends the determination of troponins at baseline, at the end of 250 mg of anthracyclines or 3 months of trastuzumab, and from there after 50 mg of anthracycline or every 3 months of trastuzumab.[15]

Subclinical LV Dysfunction with Global Longitudinal Strain guide to therapy

GLS-guided heart failure therapy is less studied. A small, observational, non-randomized study enrolled 159 patients receiving anthracycline, trastuzumab or both. Fifty-two patients showed a decrease in GLS> -11% at 6 months after baseline evaluation.[30,31] Of 52 patients, 24 were treated with beta-blockers and 28 with placebo. After 6 months of treatment, GLS and LVEF significantly improved in the beta-blockers group, but not in the placebo group. The Strain SUrveillance During Chemotherapy for Improving Cardiovascular OUtcomes (SUCCOUR) study will give some answers. Indeed, in this study in progress, patients with a relative reduction of GLS by ≥12% are treated with cardioprotective therapy. According to the position paper of the Working Group on Cardio-oncology of the European Society of Cardiology, ACE inhibitors and beta-blockers are recommended in patients with asymptomatic cardiac dysfunction to prevent the development of symptomatic heart failure or further dysfunction. This recommendation is based on an observational study, enrolling 2625 patients treated with anthracycline. In the population developing cardiotoxicity (n=226; defined by a decrease of 10 percentage points to a value <50%), ACE inhibitors +/– beta-blockers were initiated early. Among these 226 patients, 82% recovered from cardiotoxicity at least partially with heart failure therapy. Nevertheless, those who failed to improve LVEF had a significantly higher risk of major cardiovascular events. These findings support the fact that early detection of subclinical cardiac dysfunction by LVEF decrease could lead to an early start of heart failure therapy, thus preventing cardiac outcomes *(Figure 1)*.[32-35]



Before chemotherapy GLS–22% 6 months after GLS–14% 3 months after BB GLS–18%

Figure 1: Illustrates a case with subclinical left ventricular dysfunction, and comparison GLS before and after cardioprotective therapy.

CONCLUSION

The global longitudinal deformation can be a more reproducible early method of ventricular mechanics. Much still remains to be understood about the role of different imaging methods in the identification and management of cardiotoxicity by chemotherapy. The long-term effect of those early changes we are now finding is still not understood, but certainly the prognostic significance of those abnormalities in cancer survivors or those who have received radiation therapy should be clarified to allow for early interventions that can change the natural history of cardiotoxicity The primary objective for the cardio-oncological group is through these advanced techniques to identify patients and identify those at high risk for cardiotoxicity.

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